

DEREPLICATION OF CYTOTOXIC CUCURBITACINS IN PLANT EXTRACTS

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Drugs based on compounds isolated from plants form a major part of the pharmaceutical armamentarium against cancer,¹ and plants are an excellent source of pharmaceutical leads.² As part of an ongoing search for novel natural product anticancer agents, plant samples are collected, mainly from tropical forests, and a portion is extracted and screened in a panel of human cancer cell lines.³ Extracts that show cytotoxic activity in the cell-line panel are then prioritized for bioassay-guided fractionation and identification of the active components.³ The process of isolating active compounds is time-consuming, and can potentially result in the isolation of one or more known compounds with little or no potential for development as anticancer drugs.⁴ A number of approaches have been employed to “dereplicate” extracts prior to full-scale extraction and isolation work (i.e., to try to avoid the replication of previous isolation work).⁵ Several hundred extracts have been analyzed using a previously reported HPLC-MS dereplication method, in which, biological activity is correlated with molecular weight information, which can be used to survey the phytochemical literature for compounds that match the active components of the extract.^{3,5} This method provides a chemical rationale for prioritizing samples, but cannot be used to identify specific compounds, without comparison with reference compounds.

In the course of the LC-MS dereplication of cytotoxic plant extracts, a number of extracts have been predicted to contain members of the cucurbitacin class of triterpenes as the cytotoxic principles. Several potentially cytotoxic cucurbitacins have been studied *in vivo* and found to have poor therapeutic indexes and little potential for further development.⁶ A modified version of the previously reported LC-MS dereplication method was used to establish LC-MS profiles for several known cytotoxic cucurbitacins using reference compounds provided by the National Cancer Institute, and this method was used to dereplicate cucurbitacin-containing extracts.

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Supported by NCI/NIH Grant U19 CA52956.

